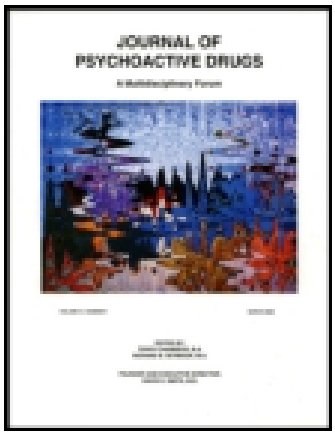

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Immunological Effects of Ayahuasca in Humans

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Immunological Effects of Ayahuasca in Humans

Rafael Guimarães dos Santos, Ph.D.[a]

Abstract — Ayahuasca is a botanical hallucinogen traditionally used by indigenous groups of the northwest Amazon. In the last decade, the use of ayahuasca has spread from Brazil, Colombia, Ecuador, and Peru to the U.S., Europe, Asia, and Africa. Despite acute and long-term evidence of good tolerability and safety for ayahuasca administered in the laboratory or ritually consumed in religious contexts, little is known about the immunological impact of ayahuasca on humans. Since ayahuasca is used by an increasing number of consumers, and considering its therapeutic potential, more information is needed regarding ayahuasca potential risks. This article presents a brief overview of the available data regarding the immunological impact of ayahuasca in humans.

Keywords — ayahuasca, dimethyltryptamine, hallucinogens, harmine, immunomodulation

INTRODUCTION

Ayahuasca is a botanical preparation with hallucinogenic effects used by several northwestern Amazonian indigenous groups for initiatory rites, war, hunting, and healing (Luna 2011; Schultes 1998; Schultes & Hofmann 1992). Ayahuasca is also used therapeutically by Mestizo populations in Amazonian countries (Luna 2011; Schultes 1998; Schultes & Hofmann 1992), and is consumed as a sacrament by Brazilian syncretic religions (Labate & Jungaberle 2011; Labate, Rose & dos Santos 2009). In the last few decades, these Brazilian religious organizations expanded their activities in the United States, Europe, Asia, and Africa (Labate & Jungaberle 2011; Labate, Rose & dos Santos 2009).

Ayahuasca is usually prepared by the decoction of the liana *Banisteriopsis caapi* with the leaves of the shrub *Psychotria viridis* or from the liana *Diplopterys cabrerana* (dos Santos 2011; Labate & Jungaberle 2011; Luna 2011; Labate, Rose & dos Santos 2009; Riba 2003; Schultes 1998; Ott 1994; Schultes & Hofmann 1992). *D. cabrerana* is mainly used in Colombia and Ecuador, while *P. viridis* is commonly used in Ecuador, Peru, Brazil, and worldwide (dos Santos 2011; Labate & Jungaberle 2011; Luna 2011; Labate, Rose & dos Santos 2009; Riba 2003; Schultes 1998; Ott 1994; Schultes & Hofmann 1992). Plants from other genera are occasionally added to ayahuasca, but their use is generally restricted to indigenous contexts (dos Santos 2011; Labate & Jungaberle 2011; Luna 2011; Labate, Rose & dos Santos 2009; Riba 2003; Schultes 1998; McKenna, Luna & Towers 1995; Ott 1994; Schultes & Hofmann 1992).

B. caapi is rich in the β-carboline alkaloids harmine, tetrahydroharmine (THH), and harmaline, while *P. viridis* is rich in the hallucinogenic tryptamine dimethyltryptamine (DMT) (dos Santos 2011; Riba 2003; Ott 1994). Several studies report that harmine and DMT are the main active compounds in ayahuasca (dos Santos 2011; Riba 2003; Riba et al. 2003; Ott 1994). β-carbolines act as reversible inhibitors of the enzyme monoamine oxidase-A, which normally metabolizes DMT in the gut; with this enzymatic inhibition DMT is able to reach the central nervous

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system, where it acts as a 5-$HT_{1A/2A/2C}$ receptor agonist in frontal and paralimbic brain regions (dos Santos 2011; Riba et al. 2003; 2006; Riba 2003). Moreover, recent studies highlighted the importance of the glutamatergic system in the neurochemistry of the effects produced by hallucinogenic drugs (Hanks & González-Maeso 2013; Moreno et al. 2011; González-Maeso et al. 2008). The head-twitch behavioral response, a mouse behavioral proxy of human hallucinogenic action, is induced by all hallucinogenic 5-HT_{2A} receptor agonists, and this behavior is decreased in knockout mice for the metabotropic glutamate 2 (mGlu2) receptor (Hanks & González-Maeso 2013; Moreno et al. 2011). Furthermore, this receptor has been shown to be expressed in close molecular proximity with the 5-HT_{2A} receptor in tissue culture and mouse frontal cortex (Hanks & González-Maeso 2013; González-Maeso et al. 2008).

Several non-controlled and placebo-controlled studies were performed on the acute effects of ayahuasca and suggest a good safety profile for this substance (dos Santos 2011; 2013a; Riba et al. 2003; 2006; Riba 2003). Longitudinal studies on the long-term consequences of ayahuasca consumption also suggest safety (dos Santos 2013a; Barbosa et al. 2012; Bouso et al. 2012; Fábregas et al. 2010). Since ayahuasca is used by an increasing number of consumers and also considering its therapeutic potentials (Palhano-Fontes et al. 2014), more information is needed regarding ayahuasca potential risks (dos Santos 2013a; 2013b). This article presents a brief overview of the available data regarding the immunological impact of ayahuasca in humans.

METHODS

Electronic searches were performed using PubMed. The following key words were used: "ayahuasca"; OR "dimethyltryptamine"; OR "harmine"; OR "harmaline"; AND "immunity"; OR "immune." All studies published up to September 2014 were included without language restriction. The electronic searches obtained a total of four published papers. Inclusion criteria were: (1) double-blind, placebo-controlled clinical trials of acute ayahuasca administration; and (2) studies of long-term ayahuasca consumption. Exclusion criteria were: (1) in-vitro studies; and (2) animal studies. Searches were also performed using specialized books and book chapters, as well as doctoral theses.

RESULTS

Electronic searches obtained a total of four published papers, but only two met the inclusion criteria. The excluded studies included an in-vitro study and a review. The selected papers included two studies performed by our group that evaluated the acute impact of ayahuasca on the human immune system (dos Santos et al. 2011; 2012; dos Santos 2011). In all studies performed by our group, ayahuasca was imported from Brazil, where it was prepared using only *B. caapi* and *P. viridis*. The brew subsequently underwent a freeze-drying process that yielded a powder which was subsequently homogenized and analyzed for alkaloid contents (dos Santos et al. 2011; 2012; dos Santos 2011; Riba et al. 2003; 2006; Riba 2003).

In the first study, a double-blind, randomized, crossover clinical trial assessed the impact of ayahuasca in terms of subjective, neurophysiological, autonomic, neuroendocrine, and immunomodulatory effects (dos Santos et al. 2011). The study compared an oral dose of encapsulated freeze-dried ayahuasca (1.0 mg DMT/kg body weight) versus a placebo and an active control (20 mg *d*-amphetamine) in a group of 10 healthy volunteers. The freeze-dried material contained 8.33 mg DMT, 14.13 mg harmine, 0.96 mg harmaline, and 11.36 mg THH per gram. Measures were obtained before and at regular time intervals until 12 h after drug administration. Ayahuasca produced a significant decrease in total lymphocyte percentages versus placebo and versus amphetamine. CD3 and CD4 lymphocyte levels were significantly decreased after ayahuasca and amphetamine versus placebo. CD19 levels were not modified by any treatment in the global analysis, but the time course analysis found a significant decrease after ayahuasca at two hours. Natural killer cell (NK) levels were significantly increased after ayahuasca and amphetamine versus placebo. No differences were observed between treatments at 24 h, suggesting transient effects.

In the second study, a double-blind, randomized, crossover clinical trial assessed the possible occurrence of tolerance or sensitization after two consecutive oral ayahuasca doses (freeze-dried, 0.75 mg DMT/kg body weight each dose) (dos Santos et al. 2012). The freeze-dried material contained the same alkaloid concentration from the previous study (dos Santos et al. 2011). Subjective, neurophysiological, cardiovascular, autonomic, neuroendocrine, and cell immunity measures were obtained before and at regular time intervals until 12 h after first dose administration. Similar to our previous study (dos Santos et al. 2011), significant decreases in CD3 and CD4 lymphocyte levels and significant increases in NK cell levels were reported after ayahuasca. No tolerance or sensitization was observed for any of the studied immunological variables.

The only long-term data found in the bibliographical research was a book chapter reporting a clinical evaluation of 15 long-term (at least 10 years) members of a syncretic church that utilizes ayahuasca as sacrament, compared with 15 matched controls with no prior history of ayahuasca ingestion (Andrade et al. 2004). Church members typically consume ayahuasca twice monthly, but often several times per week (Labate, Rose & dos Santos 2009). Membership requires complete abstinence from all other psychoactive substances. Immunity data was collected before ayahuasca

ingestion. This study reported no significant differences in the blood analysis regarding total leucocytes between long-term ayahuasca consumers and controls.

DISCUSSION AND CONCLUSIONS

The main immunological findings in the acute studies on the human pharmacology of ayahuasca were transient reductions in CD3 and CD4 cell levels and enhanced NK cell levels. The main long-term finding was an absence of significant differences in the blood analysis regarding total leucocytes between long-term ayahuasca consumers and controls.

Hallucinogenic compounds like LSD and psilocybin share a common mechanism of action with DMT, the main psychoactive substance in ayahuasca: agonist activity at the serotoninergic 5-$HT_{1A/2A/2C}$ receptors and action on the metabotropic glutamate 2 (mGlu2) receptor (Hanks & González-Maeso 2013; dos Santos 2011; Moreno et al. 2011; González-Maeso et al. 2008; Riba 2003; Nichols 2004). One study found decreases in CD8 lymphocytes following the administration of 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI, a 5-HT_{2A} receptor agonist) to mice, and this effect was antagonized by the 5-HT_{2A} antagonist ketanserin (Davydova et al. 2010). Although no significant changes in CD8 percentages were found in the acute studies of ayahuasca administration (dos Santos et al. 2011; 2012), this study in mice indicates that serotonergic hallucinogens can modulate the immune function using a direct mechanism. 5-HT_{2A} receptors are known to be expressed in central and peripheral immune-related cells (Nau et al. 2013; Stefulj et al. 2000). DMT may be directly activating both central and peripheral 5-HT_{2A} receptors on leukocytes and other immune cells and tissues, impacting their differentiation, function, and ability to secrete cytokines, resulting in the observed differences in CD3, CD4, and NK cells. A recent study with DOI further supports this hypothesis (Nau et al. 2013). DOI produced anti-inflammatory effects in mice by blocking TNF-α-induced expression of pro-inflammatory cell adhesion (Icam-1, Vcam-1), cytokine (IL-6, IL-1b), and chemokine (Mcp-1, Cx3cl1) genes, and expression of VCAM-1 protein. These effects were blocked by a 5-HT_{2A} selective antagonist.

Although a potentially direct 5-$HT_{1A/2A}$-receptor-mediated action could partially explain the observed effects produced by ayahuasca, another possibility is that activation of the sympathetic nervous system (SNS) and cortisol release could modulate lymphocyte distribution (Friedman & Irwin 1997). It has been suggested that the immunomodulatory changes produced by LSD could be the result of a nonspecific stress response on the adrenal glands, produced by an indirect mechanism involving the hypothalamic-pituitary-adrenal (HPA) axis and the SNS (Hintzen & Passie 2010; House, Thomas & Bhargava 1994; 1997; Sackler, Weltman & Owens 1966; Weltman & Sackler 1966; Hollister & Sjoberg 1964; Sackler, Weltman & Sparber 1963; Feld, Goodman & Guido 1958; Forrer & Goldner 1951). LSD can cause lymphopenia, eosinopenia and neutrophilia in animals (Hintzen & Passie 2010; Weltman & Sackler 1966; Sackler, Weltman & Sparber 1963). In-vitro studies reported that LSD suppresses the proliferation of B lymphocytes, inhibits the induction of cytotoxic T lymphocytes, and also inhibits the production of the cytokines interleukin IL-2, IL-4, and IL-6 (House, Thomas & Bhargava 1994; 1997). Regarding NK cells, LSD produces a dose-dependent effect: low doses enhance both basal and IL-2 augmented NK cells, while higher doses suppress NK cells (House, Thomas & Bhargava 1994; 1997). LSD can produce neutrophilia and eosinopenia in humans, although the data on eosinopenia is contradictory (Hintzen & Passie 2010; Hollister & Sjoberg 1964; Feld, Goodman & Guido 1958; Forrer & Goldner 1951). Psilocybin, a compound related chemically and pharmacologically to DMT and LSD, can produce leucopenia in humans (Passie et al. 2002).

In humans, DMT (Strassman, Qualls & Berg 1996; Strassman & Qualls 1994) and psilocybin (Hasler et al. 2004; Passie et al. 2002) can increase cortisol and adrenocorticotropic hormone (ACTH) levels, stimulating the HPA axis. Moreover, ayahuasca produces significant increases in cortisol levels (dos Santos et al. 2011; 2012; Callaway et al. 1999) and in the urinary excretion of normetanephrine, a noradrenaline metabolite (Riba et al. 2003), which suggests stimulation of the HPA axis and of the SNS, respectively.

Moreover, the overall time-dependent neuroendocrine and immunological profile observed after acute ayahuasca administration is similar to that observed in humans under stress (Van de Kar & Blair 1999; Breznitz et al. 1998). Increased glucocorticoid levels and lymphocyte redistribution in acute stress have traditionally been regarded as immunosuppressant (Friedman & Irwin 1997), although more recent views emphasize that, contrary to chronic stress, acute stress may have modulatory rather than inhibitory effects on immunity (Dhabhar 2009).

Further evidence on the nonspecific nature of ayahuasca effects is the similarity with the profile of immunological changes induced by psychostimulants like *d*-amphetamine (dos Santos et al. 2011) and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) (Pacifici et al. 2000; 2001), which basically involve decreases in CD3 and CD4 T lymphocytes and increases in NK cell levels.

DMT could modulate the immune system by other mechanisms. A recent study (Frecska et al. 2013) reported a significant increase in the levels of secreted interferon-γ and interferon-β in cultures of human NK cells and

dendritic cells after DMT administration *in vitro*, and suggested that this effect could be mediated by the sigma-1 receptor. This effect was consistent with further findings showing an increase in type I and type II interferon gene expressions in these cells, which was not associated with alterations in the mRNA and protein levels of inflammatory cytokines. More recently, a study investigated the effects of DMT and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) on sigma-1 receptors in human myeloid immune cells under inflammatory conditions (Szabo et al. 2014). DMT and 5-MeO-DMT reduced the mRNA and the secreted levels of the pro-inflammatory cytokines IL-1β, IL-6, TNFα and the chemokine IL-8, while increased the secretion of the anti-inflammatory cytokine IL-10. Both drugs abolished the capacity of human myeloid cells to initiate adaptive immune responses mediated by inflammatory T helper 1 (Th1) and T helper 17 (Th17) cells. Gene knock-down experiments showed that silencing the sigma-1 receptor ablated the modulatory potential of DMT and 5-MeO-DMT on TNFα and IL-10 secretion and on Th1/Th17 responses.

Another study (Tourino et al. 2013) reported that DMT increased the cytotoxic activity of peripheral blood mononuclear cells, suggesting a more effective tumor-reactive response by these cells. Furthermore, an in-vitro study (Gomes et al. 2014) reported that DMT was detected in the supernatant of a melanoma cell line and that DMT oxidation was catalyzed by peroxidases. The authors suggested that since peroxidase activity is broadly found in inflammatory conditions, DMT metabolization could be relevant in diseases in which inflammation is present.

Regarding β-carbolines, a study reported that in-vitro exposure to harmaline results in dose-related suppression of IL-2 and IL-4 production, cytotoxic T lymphocytes (CD8 lymphocytes) activity, B cell proliferation, and NK cell activity, but does not alter macrophage function (House, Thomas & Bhargava 1995). Harmine, harmaline, and THH are reversible inhibitors of monoamine oxidase-A; THH also acts as a selective inhibitor of serotonin reuptake (dos Santos 2011; Riba 2003; Buckholtz & Boggan 1977). The inhibition of monoamine oxidase and serotonin reuptake may increase serotonin levels; serotonin may affect immunity through different receptors (Nau et al. 2013; Davydova et al. 2010; Idova et al. 2008; Stefulj et al. 2000). Furthermore, alkaloids or other compounds unknown and uncharacterized in ayahuasca may be acting in the immune system through serotonergic-independent mechanisms.

The health impact of ayahuasca ingestion in terms of susceptibility to disease is difficult to ascertain with the available data. Lymphocytes are the main cellular components of the immune system and lymphocyte deficiencies may predispose to infectious diseases. CD4 cells regulate cytotoxic T cells such as CD8 lymphocytes, which in turn destroy cells infected with intracellular microbes; CD4 cells also regulate B lymphocytes (CD19), which are responsible for antibody secretion (Chaplin 2010). Some viral infections, such as that caused by the human immunodeficiency virus, may cause sustained and marked decreases in some T-cell subpopulations (CD4 lymphopenia). Therefore, reductions in CD3 and CD4 are usually interpreted as detrimental, potentially leading to deleterious effects by decreasing the body's ability to fully destroy infected cells and to produce antibodies (Chaplin 2010). On the other hand, increases in NK cells could be beneficial, these cells being involved in fighting virally infected and cancerous cells (Caligiuri 2008; Lanier 2008). However, acute ayahuasca administration produces only transient lymphocyte redistribution, without apparent pathological significance. Regarding long-term ayahuasca ingestion, no effects on total leukocytes were reported (Andrade et al. 2004). This difference could be explained by the fact that ritual ayahuasca consumption usually occurs bimonthly (Labate, Rose & dos Santos 2009), theoretically allowing a recovery of the immune system until the next ayahuasca intake.

Limitations of the studies of acute ayahuasca administration include small sample size and multiple comparisons. However, results were remarkably similar in both studies. The main limitations of the long-term study are the lack of control over the ingested dose, the small sample size, and the assessment of total leukocytes as the only immunological parameter. Nevertheless, this is the only immunological study investigating long-term ayahuasca use. Considering the increasing popularity of ayahuasca and that ingestion of this substance on a regular basis is a central feature of the ayahuasca religions, the impact of regular ayahuasca use on human immunity warrants further investigation.

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